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HIV-infected women on antiretroviral treatment in Uganda have increased mortality during pregnant and postpartum periods

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Abstract

Objective—To assess the impact of pregnancy on mortality among HIV-infected Ugandan women initiating antiretroviral therapy (ART).

Design—Prospective cohort study.

Methods—HIV-infected women initiating ART in the Uganda AIDS Rural Treatment Outcomes study were assessed quarterly for self-reported pregnancy. The association between pregnant/postpartum ("pregnancy-related") follow-up periods and mortality was assessed with Cox proportional hazards models adjusted for age, CD4 cell count, plasma HIV-1 RNA levels, and ART duration.

Results—354 women with median age 33 years (IQR: 27-37) and CD4 142 cells/mm^3 (IQR: 82-213) were followed for a median of 4.0 years (IQR: 2.5-4.8) after ART initiation, with 3% and 6% loss-to-follow-up at years 1 and 3. 109 women experienced pregnancy. Five deaths occurred during pregnancy-related follow-up and 16 during non-pregnancy-related follow-up, for crude mortality rates during the first year after ART initiation of 12.57/100 PYs and 3.53/100 PYs (Rate Ratio 3.56, 95% CI: 0.97-11.07). In adjusted models, the impact of pregnancy-related follow-up on mortality was highest at ART initiation (aHR: 21.48, 95% CI: 3.73 - 123.51), decreasing to 13.44 (95% CI 3.28 – 55.11) after 4 months, 8.28 (95% CI 2.38 – 28.88) after 8 months, 5.18

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(95% CI: 1.36 - 19.71) after one year, and 1.25 (95% CI: 0.10 - 15.58) after two years on ART. Four of five maternal deaths occurred postpartum.

Conclusions—Pregnancy and the postpartum period were associated with increased mortality in HIV-infected women initiating ART, particularly during early ART. Contraception proximate to ART initiation, earlier ART initiation, and careful monitoring during the postpartum period may reduce maternal mortality in this setting.

Keywords

HIV; maternal health; maternal mortality; immune reconstitution; pregnancy; postpartum; antiretroviral therapy; mortality; Africa; women

Introduction

HIV-infected women have a higher risk of maternal mortality compared to women without HIV [1-4], with a recent meta-analysis reporting an eight-fold increased risk of death during pregnancy or postpartum periods [5]. In 2011, there were an estimated 56,100 HIV-related maternal deaths, accounting for approximately 20% of maternal deaths worldwide [1]. HIV infection has been principally associated with indirect causes of maternal death such as increased susceptibility to opportunistic infections during pregnancy and the postpartum period, particularly among women without access to antiretroviral therapy (ART) [2, 4, 6-10].

Among women living with HIV, several studies have investigated whether pregnancy confers an independent risk of mortality. A meta-analysis of studies conducted among women not taking ART suggested an increased odds of death (aOR 1.8 (95% CI 0.99, 3.30)) and HIV disease progression (aOR1.41 (95% CI 0.85, 2.33)) among pregnant HIV-infected women compared with non-pregnant HIV-infected women, with higher risks among women in resource-limited countries [11].

Whether pregnancy remains independently associated with an increased risk of death among HIV-infected women on ART is not known. The few studies evaluating crude mortality rates or proportion of deaths among HIV-infected women on ART show no effect of pregnancy on mortality risk [12, 13], or in some cases, a protective effect (although this was limited to women with CD4 cell count between 200-500 cells/mm^3; no difference was observed between women with CD4 cell count below 200 cells/mm^3) [14]. The studies reporting no effect had high (> 20%) losses-to-follow-up, which might have led to underestimation of maternal mortality. In addition, women who are biologically capable of pregnancy may be healthier than women who cannot get pregnant [15, 16]. Thus, comparing overall mortality of HIV-infected women with or without pregnancy without rigorously adjusting for disease stage may underestimate pregnancy-related mortality. Moreover, comparing mortality rates without accounting for the time-limited effects of pregnancy may dilute time-specific effects of pregnancy on mortality.

To address these issues, we assessed the impact of being pregnant or up to one year postpartum on mortality among HIV-infected Ugandan women initiating ART in a cohort

study with a high level of retention and vital status ascertainment. The cohort is limited by sample size but strengthened by detailed follow-up to allow for classification of women as pregnant or postpartum, alive or dead. Understanding whether pregnancy affects mortality risk among HIV-infected women on ART is critical to optimizing HIV treatment and reproductive health programming for women living with HIV, particularly in settings with high baseline maternal mortality.

Methods

Setting

The Mbarara District of Uganda is a primarily rural setting located approximately 265 kilometers southwest of the Ugandan capital city of Kampala. Regional adult HIV prevalence is estimated at 10% [17]. The Mbarara University HIV clinic offers comprehensive HIV care services, including ART, at no cost to patients, provided through the Ugandan Ministry of Health with support from the President's Emergency Plan for AIDS Relief (PEPFAR), the Global Fund, and the Family Treatment Fund [18].

Study Participants

Study participants were sampled from the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort study of over 700 HIV-infected adults initiating their first ART regimen at the Mbarara University HIV clinic. Participants have quarterly study visits with structured interviews and real-time laboratory testing (CD4+ T cell count and plasma HIV-1 RNA level). For this analysis of pregnancy and mortality, we restricted the sample to 18-49 year old women enrolled from June 2005 and followed through September 2011.

Measurements

The primary outcome was death as assessed through active vital status ascertainment. When cohort participants miss a scheduled study visit, study staff attempt to reach the participant via phone or home visit. If contact is not successful within 6 months, study staff attempt to ascertain participant vital status through review of records in the referring HIV clinic and communication with the participant's family. For participants who die, cause of death is investigated through communication with families and caregivers and, when available, review of clinic and hospital records.

The primary predictor variable was pregnancy status, which we classified as being pregnant or up to one year postpartum (“pregnancy-related”), or being neither pregnant nor postpartum (“non-pregnancy-related”). Periods of pregnancy were defined based on self-report in structured quarterly interviews. Pregnancy start was considered to be the date pregnancy was first reported and pregnancy end was the subsequent date at which women reported no longer being pregnant. For eight women who reported a live birth and for whom the period of pregnancy based on the above calculation was <7 months (and in one case >11 months), live birth date was used to back-calculate a start date to account for a 9 month gestation. The postpartum period was defined as the period from end of pregnancy up until 12 months after the pregnancy outcome, including live birth, termination/stillbirth/miscarriage, or no longer pregnant without further specification of the pregnancy outcome.

Women entering the study reported whether they were currently pregnant but did not report on dates of pre-enrollment pregnancy or postpartum status. Thus no women were counted as postpartum at study entry. Due to quarterly follow-up, there was insufficient date precision to reliably distinguish between deaths occurring within the first 42 postpartum days (early postpartum deaths) and those occurring between 42 and 365 days postpartum (late postpartum deaths) [19]. The postpartum period was therefore defined as the end of pregnancy up until 12 months after pregnancy outcome, consistent with the W.H.O. definition of late maternal mortality [19].

Analysis

Baseline characteristics of women with prevalent or incident pregnancies were compared to women with no pregnancies using Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables. Crude mortality rates were calculated using person-time methods and are reported as the number of deaths per 100 person years of follow-up (PY). We compared crude mortality rates using confidence intervals for rate ratios constructed using the Poisson distribution and test-based methods [20]. Loss to follow-up was defined as having unknown vital status 6 or more months after the last time the participant was known to be alive.

We modeled mortality using Cox proportional hazards regression with time-dependent covariates to assess the effect of being pregnant or postpartum compared to non-pregnancy related follow-up. Time-updated predictor variables included age, CD4+ T cell count, and viral load suppression (HIV-1 RNA < 400 $\log_{10}$copies/mL). We evaluated time on ART as a potential effect modifier of the relationship between pregnancy and mortality with the hypothesis that the effect of pregnancy-related periods on mortality might be strongest during early ART. An Akaike information criterion approach was used to determine the inclusion of time on ART as an effect modifier in the model. Women who had a gap of at least 6 months in cohort follow-up (i.e. women who left the study for extended periods of time, but returned) were censored to protect against pregnancy status misclassification and allowed back into the analysis upon return to the study.

Sensitivity analyses

There were 4 deaths occurring more than 6 months after last study visit (range 7-39 months) in women who were neither pregnant nor postpartum at last visit. Since pregnancy could not be excluded prior to death in these cases, they were censored from the primary analysis. We completed a sensitivity analysis in which these women contributed to non-pregnancy-related follow-up.

We also completed a sensitivity analysis to evaluate mortality during pregnancy and 90-day postpartum time periods, compared with non-pregnant time periods. The 90-day postpartum time-period allows a narrower window than one year postpartum and is feasible given quarterly follow-up of participants [15].

Data were analyzed with SAS version 9.3 (Carey, NC).

Ethics

All procedures were approved by institutional review boards at Mbarara University of Science Technology (Mbarara, Uganda), Massachusetts General Hospital/Partners Healthcare (Boston, USA), and the University of California, San Francisco.

Results

Among 354 women contributing 1215 PY of follow-up, pre-ART initiation median values were: age, 33 years (interquartile range [IQR] 27-37); CD4+ T cell count, 142 (IQR 82-213) cells/mm^3; plasma HIV-1 RNA level, $\log_{10}$ 4.96 (IQR 4.50-5.46) copies/ml; and 3 prior children (IQR 2-5, Table 1). Over the follow-up period, 109 (31%) of women experienced at least one pregnancy with most pregnancies in the first 3 years (Figure 1). Women with a pregnancy at or subsequent to ART initiation were younger (median age 29 vs. 35 years, p<0.001) with a higher median CD4+ T cell count than those without pregnancy (162 vs. 133 cells/mm^3, p=0.019). Loss to follow-up among all women was low (3% and 7% at years 1 and 5) and did not differ among women with and without pregnancy at the time of last observation (7% vs. 8%). We applied interval censoring to 28 women (7.9%) who had extended gaps between visits, where pregnancy status could not be ascertained. Of these, two had two interval censorings and one had three interval censorings (median gap 11 (IQR 11-18) months).

There were a total of 21 deaths in the cohort, 5 during pregnancy or postpartum follow-up periods and 16 during non-pregnancy-related follow-up periods for an overall mortality rate of 1.73/100 PY. During the first year of ART, crude mortality rates were higher for pregnancy-related follow-up periods (12.57/100 person-years, PY) than for non-pregnancy-related follow-up periods (3.53/100 PY), representing an unadjusted mortality rate ratio of 3.56 (95% CI: 0.97-11.07). After the first year of ART, mortality rates declined both for pregnancy-related periods (0.82/100 person-years, PY) and for non-pregnancy-related periods (0.82/100 person-years, PY), and there was no evidence for an increase in pregnancy-related mortality in unadjusted analyses (RR: 0.99, 95% CI: 0.04 to 6.71).

After adjusting for time-updated age, CD4+ T cell count, and plasma HIV-1 RNA level (< vs. ≥400 copies/ml), women had an increased hazard of death during pregnancy-related periods of follow-up. This risk was modified by time on ART with risk highest at treatment initiation (aHR: 21.48, 95% CI: 3.73 – 123.51), decreasing to 13.44 (95% CI 3.28 – 55.11) at 4 months, 8.28 (95% CI 2.38 – 28.88) at 8 months, 5.18 (95% CI: 1.36 – 19.71) at one year, and 1.25 (0.10-15.58) at 2 years of ART. (Figure 2)

Timing and cause of death

While cause of death was investigated for all participants, definitive cause of death is not known; however, the qualitative details may be informative. Among 5 women who died during pregnancy-related follow-up periods, four were pregnant at ART initiation (Figure 3). One death occurred during pregnancy. This participant reported pregnancy 3 months before ART initiation and died 6 months after report of pregnancy (after 3 months on ART). At a clinic visit 3 weeks prior to death, she was profoundly anemic (Hb 5 gm/dL) and treated

empirically for a presumed urinary tract infection. She had not had a CD4 cell count or HIV-1 RNA testing since initiating ART.

The remaining four deaths occurred in the postpartum period, between one and five months after live birth. Two women died during hospitalization and the suspected causes of death were opportunistic infection: one had smear-positive pulmonary tuberculosis and congestive heart failure; one had suspected cryptococcal meningitis. While both of these women continued to have CD4+ T cell counts <200 cells/mm^3 prior to death, both had plasma HIV-1 RNA levels <400 copies/ml. Of the two additional women who died during postpartum follow-up, cause of death was not known.

Cause of death was unknown for 14/16 women who died during non-pregnancy-related follow-up periods. There was a wide variability in timing of death with median time 8.5 [IQR: 2.6-22.3] months after ART initiation.

Sensitivity analyses

When we included the 4 deaths among women that occurred more than 6 months after last study visit (range 7-39 months) as deaths occurring during non-pregnancy periods (as they were neither pregnant nor postpartum at last study visit), the adjusted hazard ratio during pregnancy-related follow-up remained high with aHR at ART initiation 20.43 (95% CI: 3.62, 115.43); 13.11 (95% CI 3.20 – 53.75) at 4 months, 8.30 (95% CI 2.39 – 28.86) at 8 months, 5.32 (95% CI: 1.44, 19.70) at 1 year, and 1.38 at 2 years (95% CI: 0.13, 15.09) after ART initiation.

Using 90-days postpartum as the cut-off for pregnancy-related follow-up, we observed a similar association between pregnancy-related follow-up and mortality with aHR 21.00 at treatment initiation (95% CI: 3.56-124.04), 13.46 (95% CI: 3.26 – 55.56) at 4 months, 8.51 (95% CI: 2.45 – 29.52) at 8 months, 5.45 (95% CI: 1.43-20.80) at 1 year, and 1.41 (95% CI: 0.11, 18.88) at 2 years after ART initiation.

Discussion

HIV is a major risk factor for maternal mortality in resource-limited settings, but the impact of pregnancy on mortality among HIV-infected women initiating ART has remained unclear. These data suggest that the combined pregnancy and postpartum period is an independent risk factor for death among HIV-infected women initiating ART in southwestern Uganda. The pregnancy-associated risk of mortality was greatest in the first year of ART with a steady decline that was no longer significant after the second year on treatment.

The level of maternal mortality observed in our study of HIV-infected women initiating ART is much higher than would be expected in the general Ugandan population, where baseline maternal mortality is considered high by international standards [19]. We observed 5 deaths/78 live births or 6,410 deaths/100,000 live births. This is 18 times the estimated maternal mortality rate for Uganda: 352 (215–558) deaths/100,000 live births [3]. This is also higher than mortality rates ranging from <1% to 2% reported in recent PMTCT studies

in sub-Saharan Africa where women initiated ART during the third trimester and continued until breastfeeding ceased [21-23]. However, median CD4 cell count at ART initiation in these studies was relatively high (median 336-403 cells/uL), so these women were likely at lower risk for immunodeficiency-related complications.

Several recent studies have evaluated the relationship between pregnancy and mortality in larger cohorts of HIV-infected women on ART without treating pregnancy as a time-dependent predictor. Westreich and colleagues showed no difference in the hazards of death among women with incident pregnancy compared to women without pregnancy in a Johannesburg cohort over a median follow up of 2.1 years (aHR 0.84, 95% CI .44, 1.6) [12]. Kaplan and colleagues found no difference in crude mortality rates during 5 years of follow up among 2131 ART naïve women referred for ART including 318 women with a prevalent pregnancy [24]. In the IeDEA South African network of nearly 30,000 women, women with pregnancy at ART initiation were less likely to die than women who were not pregnant during the first year of follow-up [13]. Similarly, our data do not reveal a statistically significant difference in overall unadjusted mortality risk among women with and without pregnancy over the follow-up period. Rather, the excess mortality risk is observed when the pregnant and postpartum state is treated as a time-dependent risk factor. Use of the time-dependent analysis acknowledges that time spent pregnant induces physiologic changes that may affect HIV disease progression (including relative immunodeficiency and susceptibility to infection) in a time-limited fashion and that women move into and out of pregnancy states and thus contribute to time at risk in both denominators. Another limitation of most of these larger cohort studies is high loss to follow-up [12, 13, 24], which may lead to underestimation of pregnancy-associated mortality. Some of these studies used inverse probability of censoring weighted methods to correct mortality estimates for differential losses to follow up, but these methods may not fully protect against biased inferences [25].

The majority of maternal deaths in our study occurred within seven months of ART initiation among women whose CD4 cell counts remained below 200 cells/mm^3. The pregnancy-associated risk of mortality declined with increasing ART exposure. It has long been recognized that mortality rates are particularly high in the first few months after ART initiation among HIV-infected individuals in resource-limited settings, particularly those with low pre-ART CD4 cell counts [26, 27]. This effect could be a consequence of persistent immunodeficiency or an increased risk of immune reconstitution inflammatory syndromes (IRIS). Indeed, three of the four postpartum deaths in our study may have been related to immunodeficiency or IRIS: one woman had smear-positive pulmonary TB and congestive heart failure, one had suspected cryptococcal meningitis, and one had Kaposis sarcoma lesions at her last clinic visit. The relative immunodeficiency of pregnancy and the postpartum period (i.e., via mechanisms like postpartum induction of the immunosuppressive enzyme indoleamine 2,3-dioxygensase-1 [28, 29]), could potentially explain an increased risk of immunodeficiency-related complications. Alternatively, the postpartum period may accentuate the risk of IRIS as the relative immunosuppression of pregnancy is reversed [30]. Even in the absence of HIV infection, the postpartum period may increase the risk of certain infections like tuberculosis, either through persistent immunodeficiency or IRIS [30, 31]. These effects may be more pronounced in HIV-infected women with advanced immunodeficiency at ART initiation. In a recent analysis of data

from six African sites with 636, 213 person-years of observation between 1990 and 2012, mortality among HIV-infected women who were not pregnant or postpartum fell during the post-ART compared with the pre-ART era (mortality rate ratio 0.42, $p < .0001$), however there was no significant change in the mortality risk among women who were pregnant or postpartum (mortality rate ratio 0.7, $p = .205$) [32]. These data are limited by inability to assess which women were on ART, but the findings may be consistent with our data showing persistently high mortality risk during pregnancy and postpartum periods while on ART.

The decline in pregnancy-associated risk of death with increasing duration of ART observed in our study is also noteworthy. As immune function recovers with ART, the relatively subtle immunologic effects of pregnancy may contribute less to mortality. A decline in pregnancy-associated mortality risk with time on ART was also recently reported from other cohorts of HIV-infected women on ART in Malawi and Mozambique [33].

Strengths of this study include long duration of observation, high levels of vital status ascertainment, and cause of death data. There are several limitations to this study. First, the association between pregnancy and mortality in our study was driven by just 5 deaths among pregnant or postpartum women: these results need to be confirmed in larger studies with active vital status ascertainment. Second, we relied on self-report of pregnancy. Given restrictions on pregnancy termination and cultural norms in Uganda, women are often reluctant to report early pregnancy, thus this study likely under-estimates pregnancy and therefore biases our results in the direction of the null hypothesis. Postpartum status was not captured at enrollment, thus only women who became postpartum during study follow-up contributed to postpartum follow-up time. This likely underestimates postpartum periods of follow-up and biases our results in the direction of the null hypothesis. In addition, given important differences between women with prevalent pregnancies and those without [12], we would prefer to complete separate analyses for women with prevalent and women with incident pregnancies. Due to the relatively small sample size in this cohort, we were not able to separate our analyses.

While our finding of an increased risk of mortality during pregnancy and the postpartum period among HIV-infected women initiating ART at advanced disease stages needs to be confirmed in other studies, this may represent an important finding. Pregnant HIV-infected women are appropriately initiated on ART for the health of the woman and to reduce perinatal transmission. However, if pregnancy increases women's mortality risk, these women may merit closer monitoring (particularly given high loss to follow-up in this group [13]) and further study to understand the mechanisms increasing risk. In addition, in longitudinal studies, a large proportion of incident pregnancies occur proximal to ART initiation [34, 35]. Whether increased pregnancy incidence after ART is a result of biological (e.g., improved fecundity) or behavioral change (e.g. increased sexual drive and/or fertility intentions with restored health) is not well understood but is likely due to a combination of factors [35-39]. Contraception uptake among HIV-infected women is low in Uganda (and other settings) [40, 41]. These findings provide further impetus for earlier diagnosis of HIV and initiation of ART for women with pregnancy or risk factors for pregnancy (e.g. fertility intentions, partner fertility intentions, younger age) [34, 35, 39,

42-45], promotion of contraception for HIV-infected women proximate to ART initiation, and careful monitoring during the postpartum period.

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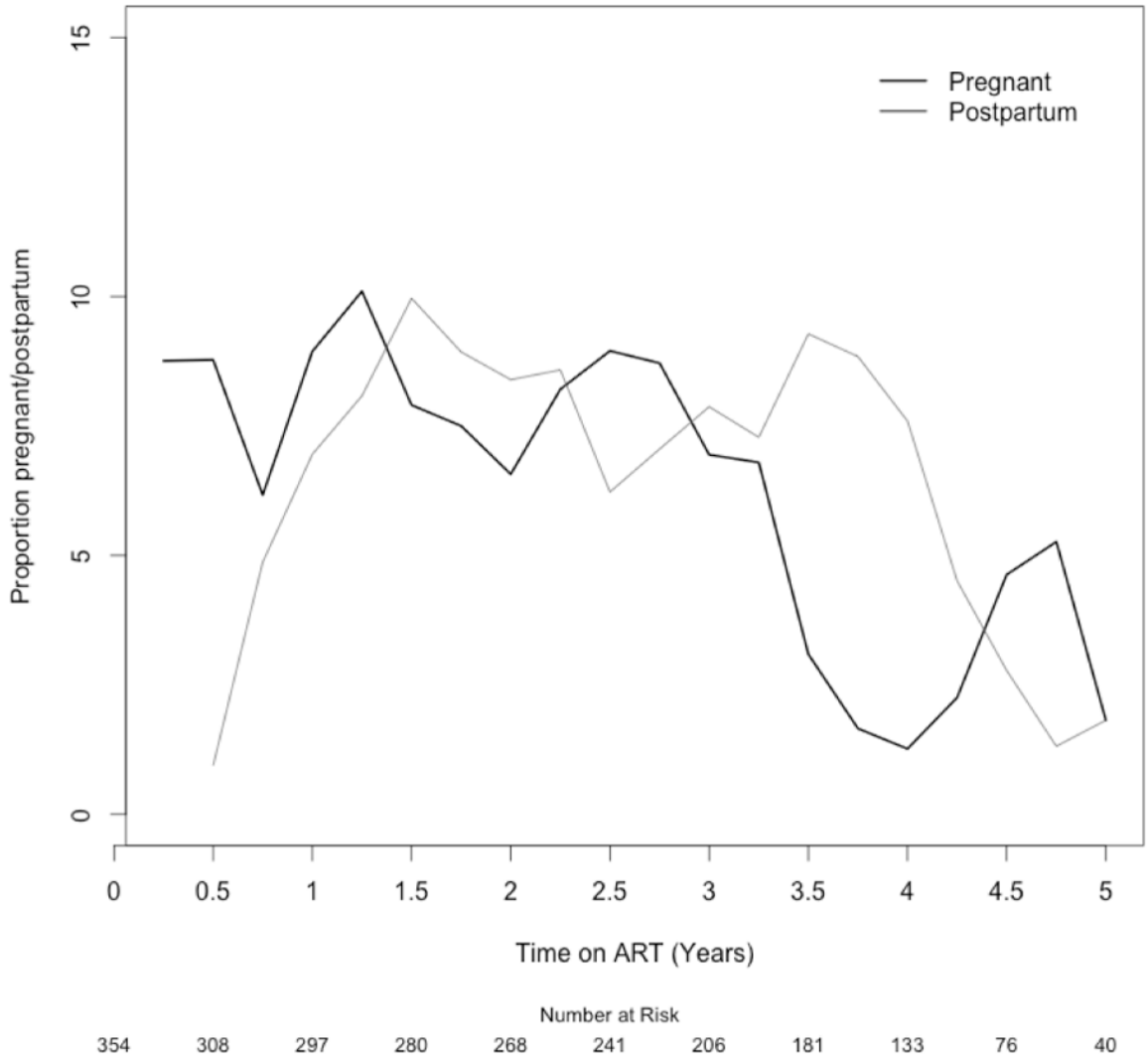

Figure 1. Proportion of women pregnant or postpartum over time

Legend: As postpartum status was not captured at enrollment, none of the women entered the study in a postpartum state. For this reason, the postpartum line begins at 0.5 years. The low number of women at risk at 5 years is due to staggered enrollment: loss to follow-up was 7% at 5 years.

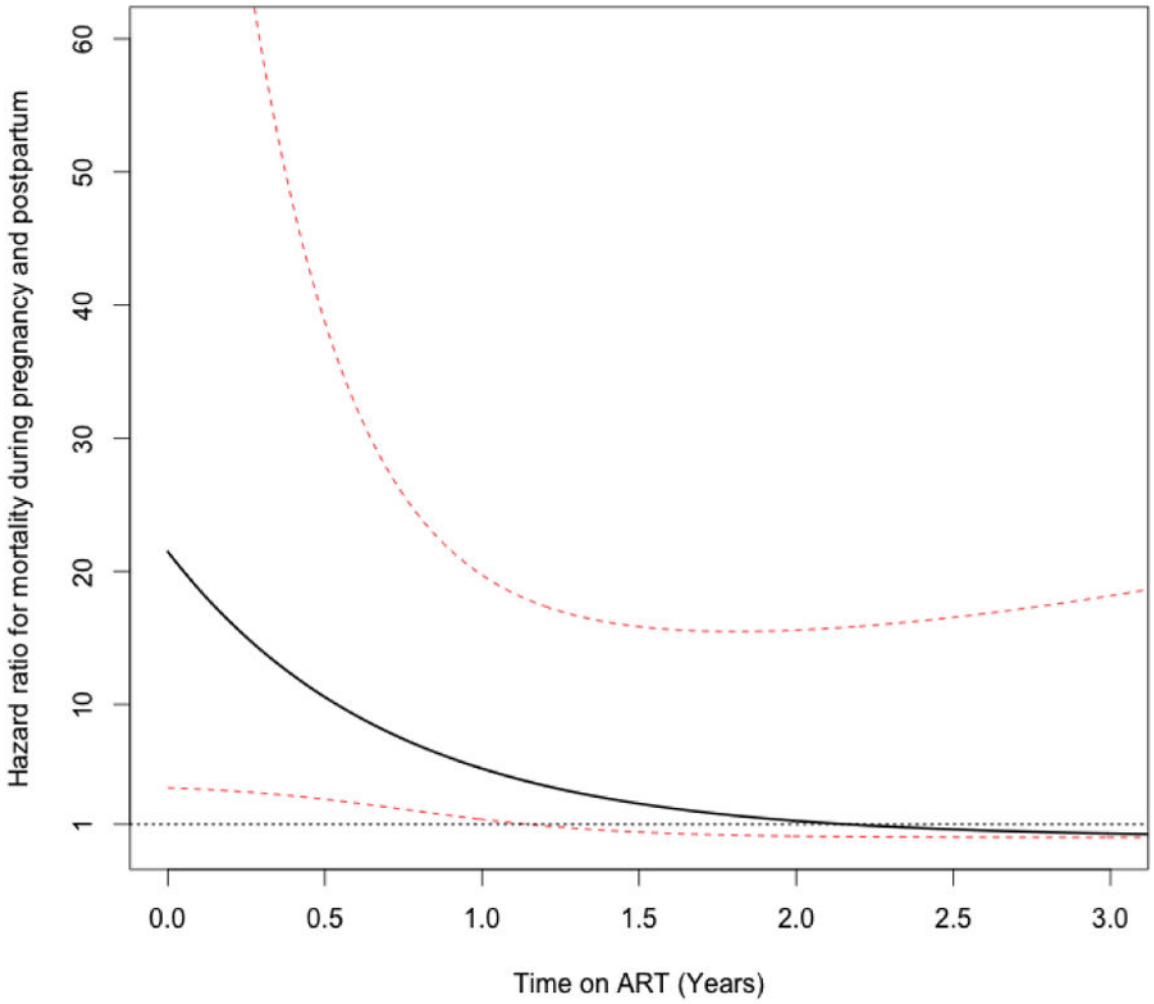

Figure 2.

Adjusted hazards ratio of death associated with pregnancy and the postpartum period modified by time on ART (95% CI shown with dashed red lines).

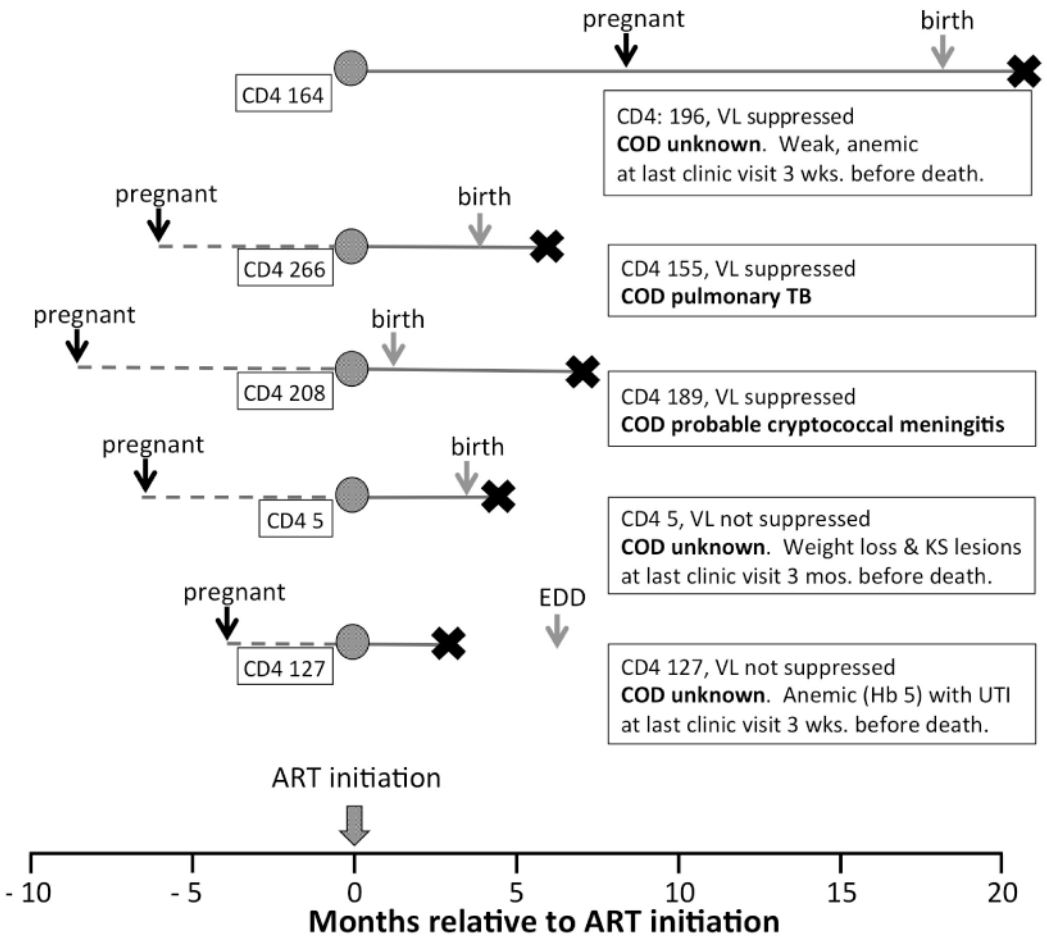

Figure 3. Timeline of pregnancy, death, and cause of death data

COD – Suspected cause of death

TB – Mycobacterium tuberculosis

KS – Kaposi's sarcoma

Hb – Hemoglobin

EDD – Estimated date of delivery

Table 1

Baseline characteristics

Variable	All Women (n = 354) Median (IQR)	Women with pregnancy (n=109) Median (IQR)	Women without pregnancy (n=245) Median (IQR)	p-value
Age (years)	33 (27-37)	29 (24-33)	35 (29 – 38)	<0.0001
CD4 cell count (cells/mm^3)	142 (82-213)	164 (90 – 245)	133 (80 – 199)	0.019
HIV-1 viral RNA (log10 copies/ml)	4.96 (4.50-5.46)	4.89 (4.43 – 5.53)	4.97 (4.54 – 5.46)	0.680
Number of children	3 (2-5)	4 (2-5)	3 (2-5)	0.579
ART Regimen				0.128
Efavirenz + 2 NRTIs	34 (9.6%)	13 (11.9%)	21 (8.6%)	
Nevirapine + 2 NRTIs	294 (83.1%)	92 (84.4%)	202 (82.4%)	
Other	5 (1.4%)	0 (0%)	5 (2.04%)	
Missing	21 (5.9%)	4 (3.7%)	16 (6.5%)	